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Роль нейротрофического фактора головного мозга (BDNF) в процессе совладания с последствиями психотравмирующей ситуации

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АННОТАЦИЯ

Обоснование. Психологическая травматизация способна вызвать заметные повреждения гиппокампа, миндалевидного тела и префронтальных отделов коры больших полушарий. Нейротрофический фактор головного мозга (англ.: brain-derived neurotrophic factor, BDNF) демонстрирует нейропротективные свойства в отношении органических повреждений головного мозга, обусловленных ишемией и черепно-мозговыми травмами. К настоящему моменту не получено достаточно оснований полагать, что BDNF также обеспечивает жизнеспособность нервной системы в процессе преодоления негативных последствий психотравмирующих событий.

Цель. Изучение взаимосвязи между индивидуально-психологическими проявлениями «устойчивого фенотипа» и содержанием BDNF в сыворотке крови индивидов, переживших психотравмирующее событие и демонстрирующих эффективное совладание.

Материалы и методы. У 33 респондентов (26 женщин, 7 мужчин, средний возраст — 26,3 ± 7,46 лет), которые в последние 3 года пережили психотравмирующее событие, исследованы уровень BDNF (с помощью метода количественного твердофазного иммуноферментного анализа), личностные и поведенческие корреляты психологической устойчивости (с помощью метода психологического опроса). Математико-статистическая обработка эмпирических данных предполагала применение корреляционного анализа и множественного регрессионного анализа.

Результаты. Содержание BDNF в сыворотке крови пострадавших служит предиктором уровня выраженности устойчивости к стрессу ($t = 2,093$, $p = 0,045$) и дезадаптивных состояний ($t = 2,511$, $p = 0,018$), проявлений посттравматического роста («Сила личности»: $t = 2,911$, $p = 0,007$; «Новые возможности»: $t = 2,242$, $p = 0,032$) и психологического благополучия ($t = -3,106$, $p = 0,004$).

Заключение. Практическая значимость проведённого исследования состоит в формировании доказательной базы клинической психологии, усовершенствовании подходов к диагностике и оказанию клинико-психологической помощи пострадавшим в результате психотравмирующих событий.

Ключевые слова: *нейротрофический фактор головного мозга; BDNF; психологическая устойчивость; психологическая травма; совладание*

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Role of brain-derived neurotrophic factor in coping with the consequences of psychotraumatic events

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ABSTRACT

BACKGROUND: Psychological trauma may cause noticeable damage to the hippocampus, amygdala, and prefrontal cortex. Brain-derived neurotrophic factor (BDNF) demonstrates neuroprotective properties in relation to organic brain damage caused by ischemia and craniocerebral traumas. To date, no sufficient evidence suggests that BDNF provides the viability of the nervous system in the process of overcoming the negative consequences of psychotraumatic events.

AIM: To analyze the relationship between the individual psychological manifestations of the "resilient phenotype" and the BDNF level in the blood serum of individuals who have psychological traumatic experience and demonstrate effective coping.

MATERIALS AND METHODS: In 33 respondents (26 women, 7 men; mean age, 26.3 ± 7.46 years) who had psychological traumatic experience in the previous 3 years, the BDNF level (determined by quantitative enzyme-linked immunosorbent assay), personality, and behavioral correlates of psychological resilience were explored (using psychological survey). Correlation and multiple regression analyses were used in the mathematical and statistical processing of empirical data.

RESULTS: The BDNF level in the blood serum of individuals with a past psychotraumatic event serves as a predictor of the level of expressiveness of resistance to stress ($t = 2.093$, $p = 0.045$), maladaptive states ($t = 2.511$, $p = 0.018$), manifestations of post-traumatic growth ("Personal Strength", $t = 2.911$, $p = 0.007$; "New Opportunities", $t = 2.242$, $p = 0.032$), and psychological well-being ($t = -3.106$, $p = 0.004$).

CONCLUSION: The practical significance of the study is attributed to the formation of evidence base for clinical psychology, improvement of approaches to diagnostics, and provision of clinical and psychological assistance to those affected by psychotraumatic events.

Keywords: *brain-derived neurotrophic factor; BDNF; resilience; psychological trauma; coping*

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ECO•VECTOR

LIST OF ABBREVIATIONS

PTSD — post-traumatic stress disorder
BDNF — brain-derived neurotrophic factor

BACKGROUND

The World Mental Health Surveys that were conducted by the World Health Organization in the participating countries revealed that the prevalence of psychological trauma (participation in military conflicts, physical and/or sexual violence, threats to the life and health of loved ones, premature violent death of a loved one, etc.) is almost 70%, wherein 5.6% are reported with symptoms of post-traumatic stress disorder (PTSD) [1]. Many people can effectively cope with the negative socio-psychological consequences of a psychotraumatic event, demonstrating psychological resilience. Scientific interest in the so-called "resilient phenotype" is developed as a "by-product" of an interdisciplinary study of disorders specifically associated with stress and trauma [2, 3]. In recent decades, a shift was found in the focus of attention from a nosocentric approach to a model focused on effective coping.

The experience in a psychotraumatic situation affects not only personal and social functioning but also the course of biochemical and physiological processes, which can lead to brain structure damages and disorders of the corresponding mental functions.

Reduction of the volume of the hippocampus is one of the most frequently reproduced and therefore reliable results of neurobiological studies of the effect of psychological trauma on the brain [4, 5]. Therefore, the left hippocampus undergoes especially pronounced changes [6]. Hypercortisolemia is considered a probable cause of an increased cortisol concentration in response to traumatic factor exposure that negatively affects the parts of the brain that is rich in corticosteroid receptors [7]. The extent of the lesion depends on the duration of psychotraumatic situation. Injury to the hippocampus is associated with the risk of PTSD symptoms, such as dissociative episodes, involuntary, and intrusive memories of the event. Another consequence of hypercortisolemia is the formation of persistent microglia sensitivity, which supports a pro-inflammatory state for a long period [8]. This condition is considered a risk factor for maladaptation during repeated psychological traumatization.

Affective disorders, which make up a special group of PTSD symptoms, may be directly related to the limbic system damage, particularly, the amygdala. D. O'Doherty et al. (2015) demonstrated that reduced volume of the amygdala (both on the left and right) is observed in all individuals who are exposed to psychotraumatic factor, regardless of their signs of PTSD [6]. Later, O.T. Ousdal et al. (2020) found that buildup of PTSD symptoms in 24–36 months after psychological trauma is associated with reduced volume of all basolateral, central, and medial nuclei of the amygdala [9].

Structural changes in the amygdala in PTSD are combined with lesions of the prefrontal cortex of the cerebral hemispheres. Thus, in patients with PTSD, a reliably significantly reduced volume of the anterior cingulate cortex on the left and right was revealed [6]. Bilateral damage to the anterior cingulate cortex can lead to a deficit in attention and effector functions, as well as to the inability to regulate affective manifestations, which is often seen in PTSD. The study by R.A. Morey et al. (2016) revealed that abused young people showing signs of PTSD have a significantly reduced volume of the right ventromedial prefrontal cortex [10]. Voxel-oriented morphometry confirmed a lower density of gray matter in the medial orbitofrontal cortex in the same sample.

Thus, a psychological trauma, regardless of its origin, can cause structural changes in the hippocampus, amygdala, and prefrontal cortex areas, which explains some of PTSD symptoms. Instrumental stimulation of these parts of the brain and pathways between them provokes decreased psychopathological symptoms and enhances patterns of coping behavior [11].

Psychological resilience manifestations may be due to:

(1) synaptic transmission suppression between the ventral hippocampus and the nucleus accumbens;

(2) activation of connections between the nucleus accumbens and the medial prefrontal cortex or basolateral amygdala;

(3) stimulation of the pathways that connect the medial regions of the prefrontal cortex and the nucleus raphes dorsalis.

Optogenetic activation methods are used for such experiments. Therefore, the question of endogenous neuroprotective factors that can contribute to recovery and effective coping with the consequences of a traumatic situation is practically unexplored.

Neurotrophins are special polypeptides that are referred to growth factors that provide the viability of the nervous system and neuronal plasticity mechanisms. A well-known representative of this family is the brain-derived neurotrophic factor (BDNF). The highest concentrations of this neurotrophin are found in the cerebral cortex, cerebellum, hippocampus, and amygdala [12]. Besides neurons, it can be synthesized in microglial

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cells, astrocytes, platelets, endothelial, and liver cells [13].

Noteworthy is the hypothesis that a high level of BDNF restores lost functions after organic brain damage [13]. An increased BDNF concentration in the blood serum of patients with closed craniocerebral trauma with the underlying intake of adaptol positively correlates with improvement of cognitive functioning and reduction of the anxiety level [14]. In turn, a low BDNF concentration in the blood serum is associated with the onset of dysregulation type cognitive impairment in patients with mild to moderate craniocerebral trauma [15]. N. V. Selyanina and Yu. V. Karakulova (2017) determined that BDNF content in the blood serum of < 300 pg/ml is a risk factor for the development of depression in the long-term period after a past brain contusion and BDNF content in the blood serum of > 600 pg/ml indicates a sufficient potential for restoration of cognitive functions [16].

Our study results of interrelations between the quantitative content of BDNF and the prognosis of recovery after brain damage caused by ischemia and trauma look encouraging. Concurrently, a natural question arises about the probable neuroprotective potential of BDNF related to organic damages provoked by psychological traumatization. The empirical data obtained nowadays do not provide an unambiguous answer to this question [17, 18].

Aim — to determine the relationship between the individual psychological manifestations of the "resilient phenotype" and the content of the BDNF in the blood serum of individuals with a past traumatic event, who demonstrate effective coping.

RESEARCH HYPOTHESIS

The BDNF can be considered a neurobiological marker of resilience and effective coping with the consequences of a psychotraumatic situation.

MATERIALS AND METHODS

The research program was approved by the Local Ethics Committee of Ryazan State Medical University (Protocol No. 10 of May 6, 2020). All respondents completed the informed consent form. Participation in the study involved a visit to a laboratory-based on the Scientific and Clinical Center of Hematology, Oncology, and Immunology (a structural subdivision of Ryazan State Medical University) to donate blood samples and fill out a set of psychodiagnostic materials that are provided by a research psychologist.

A descriptive study design was chosen, namely, correlation design with the subsequent casual modeling, which suggests the use of one experimental sample, to achieve the set aim and verify the proposed hypothesis.

The study involved 33 respondents (26 females, 7 males, with an average age of 26.3 ± 7.46 years).

The following are the inclusion criteria:

- age 18–60 years;
- history of a psychotraumatic event (loss of a dear person) that occurred no >3 years before;
- overcoming all stages of grieving and absence of signs of a prolonged pathological reaction of sorrow;
- no psychopharmacotherapy usage to achieve optimal personal and social functioning after the traumatic situation; and
- the respondent's behavior is characterized by signs of psychological resilience and effective coping with the consequences of a psychotraumatic situation that was determined in the preliminary psychological assessment.

The level of BDNF (total) in the blood serum was determined by the method of quantitative enzyme-linked immunosorbent assay of the "sandwich" type using reagents of R&D Systems (USA). Samples were analyzed on Stat Fax 4200 enzyme immunoassay analyzer following the manufacturer's instructions. The minimum detectable concentration of total BDNF range from 0.372 pg/ml to 1.35 pg/ml.

To identify the personality and behavioral correlates of psychological resilience, a survey method was used with the following standardized psychodiagnostic techniques:

1. Impact of Event Scale (adaptation by N. V. Tarabrina);
2. Brief Resilience Scale (B. W. Smith, et al.);
3. Social Readjustment Rating Scale (T. Holmes, R. Rahe);
4. Proactive Coping Inventory (adaptation by E. S. Starchenkova);
5. The COPE Inventory (version by E. I. Rasskazova, T. O. Gordeeva, and E. N. Osin);
6. Post-Traumatic Growth Inventory (adaptation by M. Sh. Magomed–Eminov);
7. The scale of Psychological Well–Being (K. Ryff);
8. Life Orientation Test (version by T. O. Gordeeva, O. A. Sychev, and E. N. Osin);
9. The multidimensional scale of perceived social support (D. Zimet);
10. Hardiness Test (adaptation by D. A. Leontiev and E. I. Rasskazova);
11. Style of Self-regulation of Behavior Questionnaire (V. I. Morosanova);
12. Multilevel personality questionnaire "Adaptability" (A. G. Maklakov and S. V. Chermyanin).

The empirical data obtained in the study were subjected to mathematical and statistical analysis using the specialized IBM SPSS Statistics 23 software. Means of descriptive statistics were used, the normality of distribution was calculated using the Shapiro–Wilk test,

as well as correlation analysis, and multiple regression analysis. The distribution of quantitatively measured data differed from normal, the dataset was subjected to a normalizing logarithmic transformation. The patterns were recognized as reliable at $p < 0.05$.

RESULTS

The normal distribution of quantitatively measured parameters was checked using the Shapiro-Wilk test. Different biological parameters were assumed to have normal distribution; in our study, the BDNF level in the blood serum. The distribution of variables that characterize the personality and behavioral manifestations of the "resilient phenotype" differs from the normal one. The obtained empirical data using psychodiagnostic techniques were subjected to a normalizing logarithmic transformation to perform the subsequent statistical calculations.

The simplest way to test the hypothesis and assess the relationship between the BDNF level in the blood serum and the individual psychological manifestations of the "resilient phenotype" is to calculate the correlation relationships. The Pearson r-test was used. The results are shown in Table 1.

Multiple regression analysis was used to determine significant interrelations between the dependent variable and predictors. The preliminary selection of dependent and independent variables was based on the results of a theoretical review of the topic and taking into account the intent of this empirical study. Thus, considering the manifestations of psychological resilience and effective coping with the consequences of a psychotraumatic situation as a dependent (resultant) variable is logical. Following the hypothesis, the BDNF is tested as an independent variable with suggested influence. Mathematical and statistical selection of variables for multiple regression analysis was conducted as follows: using correlation analysis, the absence of linear interrelations within the dataset of potential independent variables (predictors), and the presence of significant relationships between potential independent variables and a specific dependent (resultant) variable, were checked.

The combined stepwise method application of multiple regression analysis revealed the following significant patterns (Table 2).

Table 1. Results of Correlation Analysis (n = 33)

Individual Psychological Manifestations of "Resilient Phenotype" (method of evaluation)	Correlation Coefficient with BDNF level, p-level
F15 - Mental escape from the problem (The COPE Inventory)	-0.443, p = 0.01
Psychotic reactions and states (Multilevel personality questionnaire "Adaptability")	0.415, p = 0.01
Personal Strength (Post-Traumatic Growth Inventory)	0.398, p = 0.02
New Opportunities (Post-Traumatic Growth Inventory)	0.334, p = 0.05
Social support from significant others (Multidimensional scale of perceived social support)	-0.333, p = 0.05

DISCUSSION

A high BDNF level is considered one of the significant prognostic signs in the context of recovery from physical injuries associated with organic brain damage [13,16]. The results of the correlation analysis revealed that the high BDNF level is associated with the absence of psychotic state signs and moral and ethical guideline preservation ($rs = 0.415$, $p = 0.01$), and with avoidance of various ways of mental escape from the problem ($rs = -0.443$, $p = 0.01$). Correlations between the manifestations of post-traumatic growth and BDNF concentration deserve special attention. A high BDNF level is associated with the confidence of an individual in his/her ability to cope with the influence of psychological trauma ($rs = 0.398$, $p = 0.02$) and the opening of new opportunities after facing a psychotraumatic situation ($rs = 0.334$, $p = 0.05$). The negative correlation between BDNF concentration and perceived social support from significant others seems contradictory ($rs = -0.333$, $p = 0.05$). Respondents with high BDNF levels tend to underestimate the social support that they receive from the "nearest circle." This pattern may evidence that in this sample, social support from significant others is not considered a relevant resource for coping behavior.

At first glance, this individual psychological profile, compiled based on the revealed correlation relationships, fully corresponds to the theoretical concepts of a "resilient phenotype," the absence of signs of psychotic

Table 2. Results of Multiple Regression Analysis (n = 33)

The dependent variable, characteristics of the model	Independent variables	β-coefficient (standard regression coefficient)	B-regression coefficient	t emp.	p
Stress resistance (Social Readjustment Rating Scale), R = 0.749 R2 = 0.562	Involvement (Hardiness Test)	-0.742	-20.340	-5.661	0.000
	Flexibility (Style of Self-Regulation of Behavior Questionnaire)	0.345	45.040	2.549	0.016
	Brain-Derived Neurotrophic Factor	0.268	0.226	2.093	0.045
New Opportunities (Post-Traumatic Growth Inventory), R = 0.735 R2 = 0.540	Environment management (Scales of Psychological Well-Being)	0.533	0.354	4.124	0.000
	Pessimism (Life Orientation Test)	-0.342	-0.340	-2.650	0.013
	Brain-Derived Neurotrophic Factor	0.295	0.005	2.249	0.032
Personal Strength (Post-Traumatic Growth Inventory), R = 0.810 R2 = 0.656	Environment management (Scales of Psychological Well-Being)	0.523	0.246	4.169	0.000
	Brain-Derived Neurotrophic Factor	0.341	0.004	2.911	0.007
	"Human as an open system" (Scales of Psychological Well-Being)	0.427	0.191	3.225	0.003
	Preventive overcoming (Proactive Coping Inventory)	-0.286	-0.195	-2.257	0.032
Psychological Well-Being (Scales of Psychological Well-Being), R = 0.934 R2 = 0.872	Involvement (Hardiness Test)	0.318	1.570	2.731	0.011
	Proactive overcoming (Proactive Coping Inventory)	0.275	1.936	3.449	0.002
	Personal Strength (Post-Traumatic Growth Inventory)	0.368	4.334	3.903	0.001
	Risk Acceptance (Hardiness Test)	0.312	2.884	3.182	0.004
	Brain-Derived Neurotrophic Factor	-0.245	-0.037	-3.106	0.004
Maladaptation (Multilevel Personality Questionnaire "Adaptability"), R = 0.719 R2 = 0.516	Balance of affect (Scale of Psychological Well-Being)	-0.344	-0.043	-2.401	0.023
	Social support from family (Multidimensional scale of perceived social support)	0.483	1.095	3.221	0.003
	Brain-Derived Neurotrophic Factor	0.355	0.004	2.511	0.018

reactions and states in behavior, and at the same time, the presence of manifestations of post-traumatic growth [19]. However, correlation analysis established only the fact of the existence of relationships between quantitatively measured parameters, but not the tendency and nature of the influence between them.

Results of causal modeling are interpreted in the following way:

1. Predictors of stress resistance include involvement (temp = -5.661, p = 0.000), flexibility (temp = 2.549, p = 0.016), and BDNF level (temp = 2.093, p = 0.045). The term "involvement" is usually used to describe the interest and involvement of an individual in the events of his/her life and the chosen activity. The obtained model implies the manifestation of involvement within the average values, which corresponds to sufficient self-confidence, activity, and tenacity in coping with stressful situations. Flexibility is a characteristic of an individual system of behavioral activity self-regulation. The optimal level of resistance to stress, according to the obtained model, is achieved due to high parameters on the flexibility scale. A high flexibility level is manifested by the ability to quickly evaluate the meaningful conditions and easily restructure the program of actions in unforeseen circumstances, including the situation of risk. The participation of BDNF in providing resistance to stress is one of the most expected and significant results [20]. Together with the individual's involvement in life events and flexibly restructuring his/her actions, the high BDNF level forms an individual resource of stress resistance.

2. Such a component of post-traumatic growth as awareness of new opportunities is provided by BDNF (temp = 2.242, p = 0.032) and psychological variables "Environment management" (temp = 4.124, p = 0.000) and "Pessimism" (temp = -2.650, p = 0.013). One of the manifestations of the individual's post-traumatic growth is the discovery and implementation of new opportunities for personal advancement and professional self-realization. "Environment management" refers to the ability to effectively use available resources and manage the social environment to achieve personal goals. The obtained model provides a high expression level of this parameter. Concurrently, pessimism is included in the regression model with a negative coefficient, which implies a weak expression of negative expectations about the future but not the presence of optimistic attitudes.

Reasons suggest that awareness and realization of new opportunities after the psychological trauma are due to effective management of circumstances and social environment and the absence of pessimism against the sufficient neuroprotection and neuronal plasticity background.

3. Together with variables "Environment management" (temp = 4.169, p = 0.000), "Human as an open system" (temp = 3.225, p = 0.003) and "Preventive overcoming" (temp = -2.257, p = 0.032), the BDNF (temp=2.911, p=0.007) is a predictor of the expression level of personal strength. This manifestation of post-traumatic growth is associated with positive changes in self-perception and personal strength experiences. The variable "Human as an open system" describes the openness to experience, the ability of an individual to assimilate new information and form a realistic outlook on life. Preventive overcoming is a coping strategy that involves the assessment and prevention of negative events before they occur, using various coping behaviors to strengthen the tolerance for uncertainty.

According to the obtained regression model, for an individual to form a positive idea of the strength of his/her personality after psychological traumatization, the contribution of the following parameters is required: the ability to manage the environment and social situation, openness to new experience and naturalness of emotional experiences, unexpressed propensity for preventive overcoming, and neuronal plasticity, which is provided with sufficient BDNF level.

4. The regression model of the integral parameter "Psychological well-being" is distinguished by its psychometric characteristics: it explains 87.2% of the variance of the dependent variable. Psychological well-being is understood as an actual state of the individual that is characterized by the experience of the integrity and meaningfulness of his being. The results obtained indicate that the achievement of psychological well-being after a psychotraumatic event is determined by predictors such as involvement (temp = 2.731, p = 0.011), proactive overcoming (temp = 3.449, p = 0.002), personal strength (temp = 3.903, p = 0.001), risk acceptance (temp = 3.182, p = 0.004), and BDNF level (temp = -3.106, p = 0.004). The term "proactive overcoming" refers to the processes of goal setting and self-regulation in the context of coping behavior. Demonstration of proactive overcoming by an individual is aimed in general at the formation of coping resources. "Involvement" and "Risk acceptance" variables refer to the description of resilience: if involvement characterizes the degree of an individual's interest in his/her life and participation in personally significant events, then risk acceptance is the confidence that any life experience (both positive and negative) contributes to personal development. The other predictor of psychological well-being, according to this model, is just naturally personality strength, that is, the awareness and experience of the personal strength as a result of post-traumatic growth. BDNF level is included in the model with a negative sign, which suggests a secondary role of neurobiological factors to ensure psychological well-being.

5. In the study of psychological resilience and effective coping with the consequences of a psychotraumatic

situation, the description of the regression model of maladaptation is a kind of reverse side of the coin. Predictors of maladaptive disorders include "Balance of affect" (temp = -2.401, p = 0.023), social support from family (temp = 3.221, p = 0.003), and BDNF level (temp = 2.511, p = 0.018). The variable "Balance of affect" is a generalizing one and characterizes the self-esteem of an individual in different aspects, such as his/her personality, his/her abilities and competence, and interpersonal sphere. According to the model obtained, the state of maladaptation is promoted by negative self-esteem and the experience of one's powerlessness. Additionally, insufficient social support from the family perceived by an individual and the low concentration of BDNF can also be associated with the formation of a maladaptation state.

CONCLUSION

The discovered patterns should be recognized as very encouraging but their conclusions are still preliminary.

The brain-derived neurotrophic factor possessing neuroprotective properties is considered a neurobiological marker that determines effective coping with the consequences of psychological traumatization [19, 20]. The empirical study involved 33 respondents who experienced a psychotraumatic event (loss of a significant other) and showed signs of psychological resilience. The mathematical and statistical analyses results revealed that the brain-derived neurotrophic factor level in the blood serum of those affected by a traumatic event serves as a predictor of the resistance level to stress and maladaptive states, post-traumatic growth manifestations, and psychological well-being. Consequently, the brain-derived neurotrophic factor is involved in the formation of responses to psychological traumatization at the personal and behavioral levels.

Pointing out the following limitations of this study is necessary:

(1) the sample does not represent the proportion of respondents by biological gender since females with a "resilient phenotype" were more than males. Emphasizing the well-known gender specificity will be appropriate and fair for both in the genesis of psychological traumatization and the risk of post-traumatic stress disorder symptoms [1];

(2) the average age of the respondents in the sample was 26.3 ± 7.46 years. Assuming that the mechanisms that provide psychological resilience and effective coping at the neurobiological, personal, and behavioral levels will be different in individuals of other ages is logical;

(3) the sample consisted of 33 respondents. The preliminary selection of participants had signs of a "resilient phenotype," but this number is insufficient to confidently substantiate the revealed patterns.

In addition to the formal requirements for the increased number of respondents in the experimental sample and their equalization by sex and age, listing the substantive prospects for the development of this scientific direction is important. Therefore, the study of neurobiological predictors of psychological resilience and effective coping with the consequences of psychological traumatization requires careful consideration of the genetic and epigenetic regulation levels.

ADDITIONAL INFORMATION

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